VERSION OF AMENDED CLAIMS SHOWING THE CHANGES MADE:

1. (Amended) A method for expressing a heterologous gene in hepatocytes in culture comprising:

   - providing replication defective hepadnavirus particles at a titer level competent to infect hepatocytes, wherein the region of the pre-S or S-gene of the hepadnavirus genome has been replaced with the heterologous gene such that the expression of the heterologous gene is regulated by the regulatory sequences of the pre-S or the S-gene; [and]

   - infecting hepatocytes with the hepadnavirus such that the heterologous gene is delivered into the hepatocytes and expressed in the hepatocytes, and wherein the replication defective hepadnavirus particles are one of human hepatitis B virus or duck hepatitis B virus particles

2. (Amended) The method of claim [41] 42, wherein the replication defective hepadnavirus particles are human hepatitis B virus particles.

3. (Amended) The method of claim [41] 42, wherein the heterologous gene replaces [seqences] sequences of the S-gene.

4. (Amended) The method of claim [41] 42, wherein the heterologous gene replaces a region of the S-gene under control of the endogenous S-promotor.

5. (Amended) The method of claim [41] 42, wherein the heterologuous gene is inserted such that one of an authentic AUG codon of the S-gene or [its] nucleotides encoding further amino acids of the S-protein are fused in frame to the 5' end of the heterologous gene.

6. (Amended) The method of claim [41] 42, wherein the hetreologous gene encodes a modulating agent.

33. (Twice amended) A replication defective hepadnavirus particle of the group consisting of human hepatitis B virus and duck hepatitis B virus, wherein a region of a pre-S and S-gene of the hepadnavirus genome have been deleted and replaced by a heterologous gene such that the sequences for RC and RII that are essential for [producing] reverse [transcriptase] transcription are retained.

37. (Twice Amended) A pharmaceutical composition comprising:

- a replication defective hepadnavirus of the group consisting of human hepatitis B virus and duck hepatitis B virus with a region of one of its pre-S-genes or S-genes deleted and replaced with a heterologous gene such that the sequences of the RC or RII that are essential for [producing] reverse [transcriptase] transcription are [reatained] retained, and
- a pharmaceutically acceptable carrier.

39. (Twice Amended) A method of producing replication defective hepadnavirus particles of human hepatitis B virus and duck hepatitis B virus at a titer suitable for infecting hepatocytes in culture comprising:

- co-transfecting hepatocyte cells of a hepatoma cell line with:

  (i) replication defective hepadnavirus constructs, wherein a region of one of a pre S or an S-gene of the hepadnavirus DNA has been replaced with a gene encoding a heterologous gene while retaining one of an RC or RII signal, such that the expression of the gene encoding a cytokine is regulated by regulatory sequences of the S-gene; and

(iii) a helper construct for transcomplementing lacking viral gene products;

- culturing the hepatocytes until infectious viral particles are produced; and
- recovering the infectious particles.

41. (Amended) The method of claim 39, wherein the cell line is stably transfected with the helper [construct] construct and serves as a packaging cell line.

42. (Amended) A method for producing replication defective recombinant hepadnavirus particles capable of expressing a heterologous gene in hepatocytes in culture comprising:

- replacing an S-gene in a hepatitis B virus genome with the heterologous gene such that the expression of the heterologous gene is regulated by an S-promoter;
- producing a replication deficient hepadnavirus by means of a helper plasmid transcomplementing viral gene products such that the lacking viral gene products are present;
- Infecting hepatocytes with the recombinant hepadnavirus in culture, whereby the heterologous gene is delivered into the hepatocyte and expressed in the hepatocyte, wherein the replication defective recombinant hepadnavirus particles are human hepatitis B virus particles.

43. (Amended) A recombinant hepatitis B virus genome, wherein an S-gene in the genome is deleted and replaced by a heterologous gene and wherein the genome is selected from the group consisting of recombinant human

hepatitis B virus or recombinant duck hepatitis B virus, and wherein the sequences for RC and RII that are essential for reverse transcription are retained.

44. (Amended) The recombinant [HBV] genome of claim 43, wherein the heterologeous gene is under the control of the endogenous S promoter.

45. (Amended) The recombinant [HBV] genome of claim 43, wherein the heterologous gene is an immuno modulator.

46. (Amended) The recombinant [HBV] genome of claim 43, wherein the heterologous gene is a cytokine.

47. (Amended) The recombinant [rHBV] genome of claim 44, wherein the immuno modulator is selected from the group consisting of IFNα, IFNβ, IFNγ, TNFα, IL-18 or IL-12.

48. (Amended) The recombinant [rHBV] genome of claim 43, wherein the heterologous gene is a chemokine.

IN THE CLAIMS:

Canc l claim 40 without prejudice;

Amend the following claims:

Claims 2, 34, 44 and 50 insert - -. --at the end of the claim.

REMARKS

The last Office Action of November 6, 2001 has been carefully considered. Reconsideration of the instant application in view of the foregoing amendments and the following remarks is respectfully requested.

Claims 1-50 are pending in the application. It is noted that claims 2, 3, 34, 37, 41, 44 and 50 are objected to because of spelling errors. It is further noted that claims 1, 3-8, 33-41 and 49-50 are rejected under 35 U.S.C. §112, first paragraph, because of as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 1, 37-38 and 42 are rejected under 35 U.S.C. §112, first paragraph as being only enabling for a method in culture. It is further noted that claims 2-8 and 33-50 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is also noted that claims 1-8 and 33-50 are free of prior art and that the prior art did not teach or fairly suggest the presently claimed invention.

REJECTION OF CLAIMS 1, 3-8, 33-41 AND 49-50 UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Applicant has amended claims 1, 3-8, 33-41 the method for expressing heterologous genes in hepatocytes in culture. Furthermore, claim 1 has been amended to specify that the replication effective hepadnavirus particles are from HBV or DHBV (human and duck respectively).

It is believed that the rejection of the claims under 35 U.S.C. §112, first paragraph as being broader than the disclosure is thereby obviated and accordingly, withdrawal of the rejection of these claims under 35 U.S.C. §112, first paragraph is thus respectfully requested.

REJECTION OF CLAIMS 1, 37-38 AND 42 UNDER 35 U.S.C. §112, FIRST PARAGRAPH

The Examiner has also rejected claims 1, 37-38 and 42 on the grounds that the claims are broader than the disclosure. Applicant has amended the claims to set forth when the claims relate to *in vivo* and *in vitro* methods. Also the methods are defined where applicable that the hepatocytes are in culture. It is

believed that the rejection on the ground of a non-enabling disclosure has thereby been obviated with respect to these issues.

The Examiner has also questioned the limitation expressed in the claims that retention of the RII RC sequence regions are retained for the reverse transcription and encapsidation. The Examiner's attention is directed to page 5, lines 33, where a description of Figure 2 states that the replication control regions include cis- signals for pre genomic RNA synthesis and among others for reverse transcription and or encapsidation. These cis-acting sequences are thus required and are also further indicated in Fig. 2 as the RII sequence. As these reverse transcription sequences are also known in the prior art, it is believed that the recitation thereof in view of the disclosure is entirely supported.

Withdrawal of the rejection of the claims under 35 U.S.C. §112, first paragraph is thus respectfully requested.

REJECTION OF CLAIMS 2-8 and 33-50 UNDER 35 U.S.C. §112, SECOND PARAGRAPH

The rejection of claims 2-8 and 33-50 under 35 U.S.C. 2d paragraph echo those of the immediately foregoing rejection and is directed to the RC and RII regions. These regions are known in the art of reverse transcription and are cis-acting regions

Withdrawal of the rejection of these claims under 35 U.S.C. §112, second paragraph is thus likewise respectfully requested.

CONCLUSION

Applicant believes that when the Examiner reconsiders the claims in the light of the above comments, he will agree that the invention is fully supported by the disclosure.

In view of the above presented remarks and amendments, it is respectfully submitted that all claims on file should be considered supported by the disclosure, are thus patentable and should therefore be allowed.

Reconsideration and allowance of the present application are respectfully requested.

Should the Examiner consider necessary or desirable any formal changes anywhere in the specification, claims and/or drawing, then it is respectfully requested that such changes be made by Examiner's Amendment, if the Examiner feels this would facilitate passage of the case to issuance. If the Examiner feels that it might be helpful in advancing this case by calling the undersigned, applicant would greatly appreciate such a telephone interview.

The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 50-1747.

Respectfully submitted,

By: _____
Ursula B. Day
Attorney For Applicant
Reg. No: 47,296

Date: April 30, 2002
350 Fifth Avenue
Suite 3220
New York, N.Y. 10118
(212)244-5500
UBD:af